

15. Fatigue and Sleep Disorders Post ABI

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Table of Contents

Introduction	6
15.1 Sleep Disorders Post ABI	7
15.2 Fatigue Post ABI	12
15.2.1 Impact of Fatigue on Participation and Quality of Life Post ABI	15
15.2.2 Vigilance and Fatigue	18
15.3 Non-pharmacological Management Strategies	19
15.3.1 Pacing	19
15.3.2 Cognitive Behavioural Therapy.....	20
15.3.3 Acupuncture.....	21
15.3.4 Light Therapy.....	22
15.4 Pharmacological Management Strategies.....	23
15.4.1 Modafinil	23
15.4.2 Methylphenidate.....	24
15.4.3 Lorazepam and Zopiclone	25
15.5 Summary.....	26
15.6 Conclusions	27
15.7 Reference List.....	28

Table Directory

Table 15.1	Reports of Sleep Disturbance Post ABI
Table 15.2	Reports of Fatigue Post ABI
Table 15.3	Fatigue and its Impact on Participation and Quality of Life
Table 15.4	Vigilance and Fatigue Post TBI
Table 15.5	Cognitive Behavioural Therapy for the Treatment of Insomnia
Table 15.6	Acupuncture as a Treatment for Insomnia Post ABI
Table 15.7	Light Therapy as a Treatment for Sleep
Table 15.8	Modafinil Treatment for Fatigue Post ABI
Table 15.9	Methylphenidate Treatment for Sleep Disorders

Abbreviations

ABI	Acquired Brain Injury
CBT	Cognitive Behavioural Therapy
EDS	Excessive Daytime Sleepiness
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
TBI	Traumatic Brain Injury

Key Findings

Fatigue symptoms appear to be increased in individuals who sustain an ABI.

Higher levels of fatigue lead to a poorer quality of life.

Fatigue and sleep disturbances impact individuals physically, cognitively, and psychologically.

Individuals with fatigue and sleep disturbances may have increased levels of anxiety and depression.

Those with fatigue, compared to those without, were shown to have lower level jobs and more nonpaying jobs.

Fatigue related quality of life is associated with somatic symptoms of TBI and situational stress.

Fatigue experienced post-TBI has been linked to a decrease in vigilance.

Within TBI population, the relationship between vigilance and fatigue is affected and confounded by depression, anxiety, and sleep disturbances.

The effects of pacing strategies for those who have sustained an ABI are not known.

Cognitive behavioural therapy has been shown to be effective in treating insomnia related to TBI. Additional research in this area is warranted.

Acupuncture therapy has been shown to improve perception of sleep and sleep quality; however due to the small sample further research is needed.

Blue light therapy was found to reduce fatigue and daytime sleepiness; however the improvements did not persist beyond the treatment period.

Modafinil has not been shown to be effective in treating fatigue.

Modafinil has been shown to be effective short-term in treating excessive daytime sleepiness, but may also cause insomnia.

Methylphenidate does not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI when given in commonly accepted dosages.

15-Fatigue and Sleep Disorders Post ABI

Introduction

Fatigue is one of the more commonly reported symptoms associated with brain injury (Duclos et al. 2014; Elovic et al. 2005) and can exacerbate other co-morbidities. One of the greatest challenges is in properly defining fatigue; a clear definition is integral to determining how it should be measured and managed. It is believed that fatigue is a subjective experience and thus is not easily assessed by objective measures (Lewis & Wessely 1992). Individuals experiencing fatigue report it as a feeling of tiredness, weakness or exhaustion (Rao et al. 2006).

Fatigue has been defined as the *“unconscious decreased ability for physical and or mental activity due to an imbalance in availability, utilization or the retrieval of the physiological or psychological resources required to perform the activity”* p.2 (Aaronson et al. 1999). Those studying or reporting on fatigue have attempted to distinguish between physical and psychological fatigue (Aaronson et al. 1999). Physical fatigue has been defined as *“the result of excessive energy consumption, depleted hormones or neurotransmitters or diminished ability of muscle cells to contract”*p.2 (Jha et al. 2008). Psychological fatigue has been defined as *“a state of wariness related to reduced motivation, prolonged mental fatigue or boredom”* p.1 (Lee et al. 1991).

A meta-analysis conducted by Mathias and Alvaro (2012) found that 50% of people with TBI experience disturbed sleep. Common sleep complaints among individuals with moderate to severe brain injury are poor sleep quality, longer sleep-onset latency, increased nocturnal awakening, and insomnia (Duclos et al. 2014; Grima et al. 2016). Unfortunately there is large variability in the estimates of fatigue and sleep disorders within the ABI literature, much of which is due to variation in how data is collected. Both subjective and objective means of collecting this data are available. A systematic review found 16 measures of fatigue were commonly used in TBI studies (Mollayeva et al. 2013). Most common is the utilization of questionnaires, but polysomnography, actigraphy, multiple sleep latency tests, and maintenance of wakefulness tests are objective measures that may be used (Mollayeva et al. 2013).

Although it would seemingly make sense to link disorders of sleep with fatigue (Clinchot et al. 1998), this relationship remains inconclusive (Fellus & Elovic 2007). Sleep disturbances can exacerbate fatigue, however fatigue may also manifest independent of sleep disorders (Ouellet et al. 2015). There are many plausible sources of fatigue including neuroanatomical, functional, psychological, biochemical or endocrine causes (Mollayeva et al., 2013). A review by Duclos et al. (2014) suggests that sleep-wake disturbances may be due to altered circadian rhythms, damage to the cortical and subcortical structures involved, endocrine dysfunction (e.g., growth hormone or cortisol levels), pain, anxiety and depression, or the environment. This complex interplay between psychological, social, environmental and pathophysiological factors interfere with determination of the etiology of sleep disturbances (Ouellet et al. 2015). It is therefore important to investigate the medical and reversible causes of fatigue (e.g., anemia, hypothyroidism, medications that may be worsening fatigue, etc.) in patients with acquired brain injury (ABI). For those recovering from an ABI/traumatic brain injury (TBI), fatigue and sleep disorders have the ability to interfere with an individual’s ability to participate in rehabilitation programs designed to assist them in performing their activities of daily living. It also impacts one’s physical, cognitive and social abilities.

This chapter explores the problems of fatigue and sleep disorders post ABI first by reviewing studies identifying the incidence and prevalence of these symptoms, as well as by summarizing and evaluating studies of treatment interventions for each.

15.1 Sleep Disorders Post ABI

Sleep disorders tend to be classified as insomnia, excessive sleep, or excessive daytime sleepiness (EDS) (Elovic et al. 2005; Ouellet et al. 2015). It is believed that, in individuals with ABI, sleep complaints correlate with higher Glasgow Coma Scores (GCS >7) at time of injury, better immediate memory, pre-ABI presence of fatigue, a history of substance abuse, older age and female gender (Thaxton & Patel 2007). There are few studies that have investigated sleep disorders and their effects on rehabilitation post ABI (Baumann et al. 2007; Clinchot et al. 1998). It has been suggested that those who sustain a more severe TBI may underreport poor sleep, while those with a mild injury may be more aware of the changes in their sleep patterns and over report any changes that have occurred as a result of the injury (Elovic et al. 2005). Castriotta et al. (2007) found that 47% of individuals with TBI reported EDS. In a Canadian study, Ouellet et al. (2006) found, using subjective measures, that approximately 50% of their TBI sample (total n=452) reported symptoms of insomnia and those that did not report insomnia as a problem were sleeping more than before the injury. Individuals with insomnia reported having sleep difficulties 5.7 times per week (Ouellet et al. 2006). It was also noted that more than half of the individuals who reported having sleep difficulties were not being treated for the condition (Ouellet et al. 2006).

Table 15.1: Reports of Sleep Disturbance Post ABI

Author/Year Country/Study Design	Methods	Outcome
Sandmark et al. (2016) USA Case Series N=64	Population: TBI; Mean Age=50.3yr; Gender: Male=53, Female=11; Mean Time Post Injury<14d; Severity: Mild-Moderate=23, Severe=38, Unknown=3. Intervention: Retrospective chart review examining continuous electroencephalography (cEEG) for elements of sleep activity. Outcome Measure: cEEG, location of hospital disposition, Modified Rankin Scale (mRS) at hospital discharge, Intensive Care Unit (ICU) and hospital length of stay (LOS).	<ol style="list-style-type: none"> 1. Patients with features of sleep features on cEEG were more likely discharged home/to acute rehabilitation (p=0.0002), had shorter ICU and hospital LOS (p=0.058) than patients without sleep features. 2. Patients without sleep features had an increased mortality rate and were more likely to be discharged to a nursing facility (p=0.0002). 3. Multivariate analysis revealed that sleep features were independently associated with improved outcome on mRS (p=0.04).
Imbach et al. (2016) Switzerland Prospective Controlled Trial N _{Initial} =60, N _{Final} =31	Population: TBI=31, Healthy Subjects=42; <i>Experimental Group (TBI, n=31):</i> Mean Age=33.2yr; Gender: Male=20, Female=11; Mean Time Post Injury=18mo. <i>Control Group (Healthy Controls, n=42):</i> Mean Age=36.5yr; Gender: Male=31, Female=11. Intervention: As an extension to Imbach et al. (2015), patients were evaluated 18mo post-TBI for changes in sleep habits, work situation, daytime vigilance and fatigue through structured interviews. Results were compared with 6mo outcomes. Outcome Measure: Structured interview, Actigraphy (AC), Epworth Sleepiness Scale	<ol style="list-style-type: none"> 1. AC and PO revealed increase in total sleep time (p<0.005) and decrease in objective sleepiness (MSLT; p<0.00005) among patients with TBI compared to controls. 2. 67% of patients with TBI had excessive daytime sleepiness (EDS) on ESS versus 19% of controls (p<0.00005); among patients with TBI, incidence of EDS was similar at 6 and 18mo. 3. Total mean sleep time per 24hr was significantly longer for patients with TBI compared to controls (8.1hr versus 7.1hr, p<0.00005); among patients with TBI, this value was similar between 6 and 18mo.

	(ESS), Polysomnography (PO), Multiple sleep latency tests (MSLT).	<ol style="list-style-type: none"> 4. Patients with TBI underestimated prevalence of EDS on subjective measures (ESS) compared to objective measures (MSLT) at 6 and 18mo ($p < 0.0005$). 5. At 18mo but not 6mo, intracranial haemorrhage and trauma severity (GCS) were not associated with increased sleep need or objective EDS, respectively.
<p>Imbach et al. (2015) Switzerland Prospective Controlled Trial $N_{Initial}=60, N_{Final}=42$</p>	<p>Population: TBI; Gender: Male=31, Female=11; <i>TBI Group (n=42):</i> Mean Age=35.5yr. <i>Control Group (Healthy Controls, n=42):</i> Mean Age=36.5yr. Intervention: Individuals with acute TBI underwent a series of lab examinations at 5d and 6mo, as well as self-reported assessments, actigraphy and polysomnography at 6mo follow-up. Outcome Measure: Actigraphy (AC), Polysomnography (PO), Epworth Sleepiness Scale (ESS), Fatigue Severity Scale, sleep logs, Multiple Sleep Latency Test (MSLT).</p>	<ol style="list-style-type: none"> 1. According to AC and PO, patients with TBI slept longer per 24hr ($p < 0.0001$), took less time falling asleep ($p < 0.001$) and slept longer overall ($p < 0.05$). 2. Objective (MSLT), but not subjective (ESS), measures of excessive daytime sleep (EDS) were increased when compared to controls ($p = 0.001$). 3. Within the TBI group, EDS was underestimated for subjective (ESS) compared to objective (MSLT) measures ($p < 0.0005$), and sleep logs underestimated sleep times versus actigraphy ($p = 0.002$). 4. Lower GCS ($p = 0.003$) and presence of intracranial haemorrhage ($p = 0.005$) correlated with need for increased sleep in the TBI group.
<p>Gardani et al. (2015) UK Observational N=30</p>	<p>Population: TBI; Sleep Difficulties Group (n=20): Mean Age=41.6yr; Gender: Male=18, Female=2; Mean Time Post Injury=54.25mo; Mean GCS=6.42. No Sleep Difficulties Group (n=10): Mean Age=47.9yr; Gender: Male=9, Female=1; Mean Time Post Injury=14.6mo; Mean GCS=5. Intervention: Participants wore an actiwatch for 7d and completed assessments through a semi-structured interview (up to 2hr). Outcome Measure: Hospital Anxiety and Depression Scale (HADS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Barrow Neurological Institute Fatigue Scale (BNIFS), actigraphic measures: sleep efficiency (SE), sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO).</p>	<ol style="list-style-type: none"> 1. 50% of participants met diagnostic criteria for one or more sleep disorders: insomnia (26.7%), hypersomnia (6.7%), delayed sleep phase syndrome (10%), irregular sleep-wake disorder (3.3%) and periodic limb movement disorder (3.3%). 2. Individuals without sleep difficulties had improvements in actigraphic measures (SE, TST, $p < 0.05$) and a significant decrease in PSQI and ESS ($p < 0.05$); no significant associations for SOL, WASO or ISI. 3. PSQI and ISI were both significantly associated with anxiety and fatigue according to HADS and BNIFS respectively ($p < 0.01$). 4. No other significant relationships were presented for PSQI or ISI with depression, fatigue, excessive sleepiness or time since injury.
<p>Duclos et al. (2014) Canada Observational N=16</p>	<p>Population: TBI; Mean Age=27.1yr; Gender: Male=13, Female=3; Mean Time Post-Injury=18d; Mean GCS=6.56. Intervention: Patients wore a wrist actigraph beginning in the ICU and throughout their hospital stay. Actigraphy data was extracted every 3d. Other outcomes were recorded daily in the ICU post-TBI admission.</p>	<ol style="list-style-type: none"> 1. In the first 48hr of actigraphy, 25% of patients had CRAC whereas 62.5% of patients had CRAC and significant improvement in mean DAR ($p < 0.05$) in the final 48hr. 2. Higher GCS scores ($p < 0.05$), lower DRS scores ($p < 0.05$), and shorter length of stay ($p < 0.01$) improved the number of days with CRAC.

	<p>Outcome Measure: Daytime activity ratio (DAR), consolidated rest-activity cycle (CRAC), Length of ICU stay, Total length of hospital stay, Disability Rating Scale (DRS).</p>	<p>3. Total mean DAR ($p<0.01$), mean DAR of the final 48hr ($p<0.01$), DAR improvement from first to last 48hr period ($p<0.05$) and number of days with CRAC ($p<0.01$) were all associated with lower DRS scores.</p>
<p>Sinclair et al.(2014) Australia Case-Control N=42</p>	<p>Population: TBI=21, Healthy Controls=21; <i>TBI Group:</i> Mean age=44.62yr; Gender: Male=17, Female=4; Mean Time Post Injury=3.08yr. <i>Healthy Controls:</i> Mean Age=44.43yr; Gender: Male=17, Female=4. Intervention: Participants wore an actigraph and completed a daily sleep-wake diary. Outcome Measure: Sleep-Wake Diary, Nocturnal and Daily Total Sleep time (TST), Sleep onset latency (SOL), Pittsburgh Sleep Quality Index (PSQI), Wake after sleep onset (WASO), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS).</p>	<p>1. Compared to healthy controls, those with TBI had poorer sleep quality, more daytime sleepiness and more fatigue ($p<0.01$). 2. For the TBI group, daytime sleepiness (ESS) was significantly correlated with WASO ($r=0.48$, $p=0.027$). 3. For the TBI group, sleep quality (PSQI) was significantly correlated with nocturnal ($r=-0.44$, $p=0.048$) and daily ($r=-0.49$, $p=0.02$) sleep times and WASO ($r=0.52$, $p=0.028$). 4. FSS results were significantly correlated with nocturnal ($r=0.48$, $p=0.028$) and daily ($r=0.49$, $p=0.023$) sleep times.</p>
<p>Ponsford et al. (2013) Australia Case-Control N=281</p>	<p>Population: TBI=153, Healthy Controls=128; Gender: Male=184, Female=97. <i>TBI Group:</i> Mean Age=34yr; Mean Time Post Injury=9.9mo. <i>Healthy Controls:</i> Mean Age=31.3yr. Intervention: Participants completed questionnaires and a daily sleep diary. Outcome Measure: Sleep-Wake Diary, Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), General Sleep Questionnaire (GSQ), Hospital Anxiety and Depression Scale (HADS).</p>	<p>1. The TBI group, compared to healthy controls, were taking more medication (38.6% vs 19.3%), were less likely to be employed, and more likely to experience symptoms of pain, anxiety (32% versus 25%) and depression (38% versus 5%; $p<0.05$ for all). 2. Sleep quality (GSQ) was significantly worse in the TBI group ($M=5.20$) than the control group ($M=4.68$, $p=0.04$). 3. 49% of the TBI group obtained scores indicative of poor sleep quality (PSQI >5) versus 18% of controls; 33% of the TBI group had insomnia (PSQI >8) versus 3% of controls (both $p<0.0001$). 4. 24% of the TBI group reported clinically significant daytime sleepiness (ESS ≥ 10) versus 12% of controls ($p<0.01$).</p>
<p>Nakase-Richardson et al. (2013) USA Observational N=205</p>	<p>Population: TBI=205; Median Age=30yr; Gender: Male=146, Female=59; Median Time Post Injury=24d; Median GCS=7. Intervention: Rehabilitation patients assessed weekly using the Delirium Rating Scale-Revised-98 (DeIRS-R98). Outcome Measure: DeIRS-R98.</p>	<p>1. At baseline, 84% had some sleep disturbance, with 63% having moderate to severe sleep disorganization. By the third exam, rates were reduced at 59% and 28% respectively. 2. At 1mo, rates were lower than baseline but had increased slightly, 67% had some sleep disturbance and 39% had sleep disorganization or absence of sleep. 3. At 1mo, those with moderate to severe sleep disturbance, compared to those with none/mild sleep disturbance, had a longer length of stay (51.2d versus 41.7d, $p<0.001$) and duration of post-traumatic amnesia (34.7d versus 25.7d).</p>
<p>Sommerauer et al. (2013) Switzerland Case-Control N=72</p>	<p>Population: TBI=36, Healthy Controls=36; Gender: Male=52, Female=20. <i>TBI Group:</i> Mean Age=36yr; Severity: Mild=13, Moderate=7, Severe=16. <i>Healthy Controls:</i> Mean Age=36yr.</p>	<p>1. 13 participants with TBI and no controls reported daytime sleepiness (ESS >10). 2. All participants with TBI had pleiosomnia (e.g., needed at least 2hr more per 24hr than prior to injury).</p>

	<p>Intervention: Participants had a diagnostic workup in a sleep laboratory (nocturnal polysomnography).</p> <p>Outcome Measure: Epworth Sleepiness Scale (ESS).</p>	<p>3. The TBI group, compared to controls, had longer mean time asleep (9.4 versus 7.5hr, $p=0.008$), and more regular daytime naps (e.g., $\geq 5/wk$; 47% versus 0, $p<0.0001$).</p>
<p>Beaulieu-Bonneau & Morin (2012) Canada Cohort N=44</p>	<p>Population: TBI=22; Healthy Controls=22. Gender: Male=34, Female=10. <i>TBI Group:</i> Mean Age=37.46yr; Mean Time Post Injury=53mo; Mean GCS=7.23. <i>Control Group:</i> Mean Age=36.96yr.</p> <p>Intervention: Participants underwent a night of polysomnographic recording and completed several tests the next day.</p> <p>Outcome Measures: Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), Multidimensional Fatigue Inventory (MFI).</p>	<p>1. No significant between group differences were found for sleep onset latency (MWT).</p> <p>2. On the ESS 18.2% of individuals with TBI and 27.3% of controls reported clinically significant sleepiness ($p=0.47$).</p> <p>3. Compared to controls, those with TBI reported significantly higher levels of fatigue based on the MFI total score ($p<0.01$), as well as the subscales for general fatigue ($p<0.01$), mental fatigue ($p<0.001$) and physical fatigue ($p=0.03$).</p>
<p>Cantor et al. (2012) USA Observational N=334</p>	<p>Population: TBI=334; Gender: Male=229, Female=105. <i>Group 1 (n=213):</i> Mean Age=43.6yr; Mean GCS=10.5; Mean Time Post Injury=1yr. <i>Group 2 (n=121):</i> Mean Age=35.6yr; Mean GCS=9.1; Mean Time Post Injury=2yr.</p> <p>Intervention: Data abstracted from medical records. Patients then contacted for follow-up interview (60-80min) at 1yr (group 1) or 2yr post (group 2).</p> <p>Outcome Measures: Global Fatigue Index, Pittsburgh Sleep Questionnaire, Insomnia Severity Index, Diagnostic Interview for Insomnia, Sleep Hygiene Index, Epworth Sleepiness Scale, Disability Rating Scale (DRS), Functional Independence Measure (FIM).</p>	<p>1. 11% and 24% of group 1 and 2, respectively, had insomnia. Insomnia occurred and resolved in 17% of group 1 and 14% of group 2.</p> <p>2. At 1yr, predictors of insomnia were the presence of anxiety ($p<0.001$), major depression ($p=0.002$), and poor sleep quality ($p=0.005$).</p> <p>3. At 2yr, predictors of insomnia were the presence of anxiety ($p=0.016$), higher discharge cognitive FIM scores ($p=0.009$), and poorer sleep quality ($p<0.001$).</p> <p>4. At 1yr, predictors of fatigue were the presence of major depression ($p=0.007$), anxiety ($p=0.004$), greater DRS at follow-up ($p=0.011$), greater sleepiness and poorer sleep quality ($p=0.003$).</p> <p>5. At 2yr, predictors of fatigue were the presence of anxiety ($p=0.047$), abstinence from substance use ($p=0.028$), daytime sleepiness ($p=0.049$), poorer sleep quality ($p<0.001$), and insomnia ($p=0.025$).</p>
<p>Kempf et al. (2010) Switzerland Observational N=51</p>	<p>Population: TBI=51; Mean age=40yr; Gender: Male=43, Female=8; Mean Time Post Injury=3yr; Severity: Mild=21, Moderate=11, Severe=19.</p> <p>Intervention: Patients completed telephone interviews and questionnaires regarding their sleep patterns and fatigue.</p> <p>Outcome Measure: Epworth Sleepiness Scale, Excessive Daytime Sleepiness (EDS), Glasgow Outcome Scale (GOS), Fatigue Severity Scale (FSS), Hospital anxiety and depression score (HADS), Beck Depression Inventory (BDI), and International Classification of Sleep Disorders.</p>	<p>1. Sleep wake disturbance was found in 34 patients, hypersomnia in 14, EDS in 6, fatigue in 18, and insomnia in 5.</p> <p>2. Mean sleep time per day was similar at 6mo and 3yr follow-up (8.0 versus 8.2hr, respectively).</p> <p>3. 51% reported fatigue associated symptoms (day time sleepiness, lack of energy, exhaustion).</p> <p>4. A moderate correlation was found when looking at FSS scores and depression (BDI, $p=0.001$) and anxiety (HADS, $p=0.007$).</p> <p>5. GOS was associated with subjective EDS ($r=0.42$, $p=0.04$).</p>
<p>Verma et al. (2007) USA Observational</p>	<p>Population: TBI=60; Mean Age=41.03yr; Gender: Male=38, Female=22; Range of Time Since Injury=3mo-2yr; Injury Severity: Mild=24, Moderate=11, Severe=25.</p>	<p>1. ESS scores representing moderate to severe daytime sleepiness were found in 52% of patients.</p>

N=60	<p>Intervention: Patients had a neurological examination and completed a sleep-wake questionnaire. Patients underwent polysomnography (n=54) and the Multiple Sleep Latency Test (n=28).</p> <p>Outcome Measure: Epworth Sleepiness Scale (ESS), Excessive Daytime Somnolence (EDS), Hamilton Anxiety Scale (HAS), Beck Depression Inventory (BDI), Global Assessment of Functioning (GAF).</p>	<ol style="list-style-type: none"> 25% of patients reported insomnia. Of those with insomnia, 50% had sleep onset insomnia and a mean HAS score of 22.75 (mild-moderate anxiety). The remaining 50% were found to have sleep maintenance insomnia with a mean BDI score of 24.5 (moderate depression). Lower GAF scores were correlated with impaired sleep efficacy and wake during sleep ($p<0.05$).
<p>Fichtenberg et al. (2000) USA Observational N=91</p>	<p>Population: TBI=91; Mean Age=33.8yr; Gender: Male=54, Female=37; Mean Time Post Injury=3.3mo; Severity: Mild=30, Moderate=19, Severe=42.</p> <p>Intervention: Clinical assessment of sleep and mood at an outpatient clinic.</p> <p>Outcome Measure: Glasgow Coma Scale (GCS), Pittsburgh Sleep Quality Index, Beck Depression Inventory (BDI).</p>	<ol style="list-style-type: none"> In this study insomnia was associated with pain disturbance ($p<0.01$), depression ($r=0.67$, $p<0.001$) and GCS ($r=0.25$, $p<0.01$). Insomnia was associated with milder brain injury severity. 68% of those with depression (BDI score ≥ 14) had insomnia.

Discussion

The studies in the table above show that there are many different sleep disorders experienced by patients with brain injury including daytime sleepiness (Imbach et al. 2016; Imbach et al. 2015; Kempf et al. 2010; Ponsford et al. 2013; Sinclair et al. 2014), poor sleep quality, insomnia (Cantor et al. 2012; Gardani et al. 2015; Kempf et al. 2010; Ponsford et al. 2013; Verma et al. 2007), sleep disorganization (Nakase-Richardson et al. 2013), sleep wake disturbance, and hypersomnia (Gardani et al. 2015; Kempf et al. 2010). Daytime sleepiness and the increased need for sleep remains a problem in the short and long term following a brain injury (Imbach et al. 2016; Imbach et al. 2015). Even more problematic is the finding that individuals underestimate their sleep disturbances, as they report significantly less problems of excessive daytime sleepiness on subjective compared to objective measures (Imbach et al. 2016; Imbach et al. 2015).

Individuals with sleep disturbances have longer length of stay in hospital (Duclos et al. 2014; Nakase-Richardson et al. 2013; Sandsmark et al. 2016). Further, increased injury severity is associated with more disturbances in sleep and wake cycles (Duclos et al. 2014). Sandsmark et al. (2016) found that sleep disturbances recorded through electrophysiological measures were associated with unfavourable outcomes and fewer opportunities for rehabilitation. Nakase-Richardson et al. (2013) discovered that the duration of post-traumatic amnesia was longer when moderate to severe sleep disorders were present. Gardani et al. (2015) report that in severe brain injuries, insomnia and sleep quality are associated with anxiety during subacute-chronic rehabilitation. Moreover, Cantor et al. (2012) found that at one year insomnia was associated with the presence of anxiety, major depression, and poor sleep quality. Whereas, at two years, the presence of anxiety, higher discharge cognitive Functional Independence Measure scores and poorer sleep quality were predictors of insomnia (Cantor et al. 2012). Fichtenberg et al. (2000) also noted the association between insomnia, pain disturbance, and depression. A study by Wiseman-Hakes et al. (2013) supported the concept that sleep disturbances associated with TBI exacerbate cognitive, communication and mood deficits that are trauma-related. Dealing with sleep disturbances is necessary for optimal recovery.

15.2 Fatigue Post ABI

Even though fatigue has been documented to be a problem post ABI it remains understudied. Toda et al. (2006) found that individuals who had sustained a TBI reported significantly higher levels of fatigue during their time in rehabilitation than they did at 6 or 12 months post injury ($p=0.0092$). It has been hypothesized that rehabilitation itself may play a role in exacerbating feelings of fatigue and once the patient is removed from these demands and has achieved a greater understanding of their deficits the feelings of fatigue lessen. However, the literature shows that fatigue can persist for many years post injury (Bay & de-Leon 2011; Olver et al. 1996; Ouellet & Morin 2004; Rao et al. 2006).

To gain information on the severity of the problem, data is often collected through surveys, interviews or questionnaires. Comparison groups in many of the studies are those without an ABI. Scales frequently used in these surveys include the Fatigue Severity Scale (FSS), the Fatigue Impact Scale, the Visual Analogue Scale-F, the Global Fatigue Index, the Barroso Fatigue Scale, and the Epworth Sleepiness Scale; however, none of these scales were designed specifically for use in patients with brain injury, but rather they were developed for patients with Human Immunodeficiency Virus or Multiple Sclerosis (Armutlu et al. 2007; Fish et al. 2007).

Individual Studies

Table 15.2: Reports of Fatigue Post ABI

Author/Year Country/Study Design	Methods	Outcome
Chiou et al. (2016) USA Observational N=21	<p>Population: TBI=14, Healthy Subjects=7; <i>Experimental Group (TBI, n=14):</i> Mean Age=45.7yr; Mean Time Post Injury=73.3mo; Mean GCS<13. <i>Control Group (Healthy Controls, n=7):</i> Mean Age=41.1yr.</p> <p>Intervention: Participants completed neuropsychological tests measuring fatigue awareness, emotional and cognitive functioning. An informant completed the same assessments.</p> <p>Outcome Measure: Awareness Questionnaire (AQ), Beck Depression Inventory-2nd Edition (BDI-II), State Trait Anxiety Inventory (STAI), battery of cognitive tests, Modified Fatigue Impact Scale (MFIS): cognitive (MFIS-C), physical (MFIS-P), and psychosocial (MFIS-PSY) discrepancy.</p>	<ol style="list-style-type: none"> Higher levels of fatigue reported in TBI group than controls for all three subscales (MFIS-P, MFIS-C, $p<0.001$; MFIS-PSY, $p=0.006$). Cognitive discrepancy on MFIS-C was significantly higher in the TBI group versus controls ($p=0.02$); however, no significant differences observed for physical on MFIS-P or psychosocial functioning on MFIS-PSY ($p=0.11$ and $p=0.31$, respectively). Within the TBI group, MFIS-C scores were significantly greater than MFIS-P scores ($p=0.03$). Within the TBI group, anxiety on STAI was positively correlated with MFIS-P and MFIS-PSY ($p=0.005$ and $p=0.012$, respectively). Depressive symptoms on BDI-II was significantly correlated with higher MFIS-P ($p=0.037$) and MFIS-C scores ($p=0.05$).
Ponsford et al. (2012) Australia Case-Control N=217	<p>Population: TBI=139, Healthy Controls=78. <i>TBI Group:</i> Mean Age=34.72yr; Gender: Male=103, Female=36; Mean Time Post Injury=295.68d; Mean GCS=9.19. <i>Control Group:</i> Mean Age=33.38yr; Gender: Male=55, Female=23.</p> <p>Intervention: Patients completed multiple questionnaires and tests.</p> <p>Outcome Measure: Fatigue Severity Scale (FSS), Causes of Fatigue Questionnaire</p>	<ol style="list-style-type: none"> Compared to controls, those with TBI had higher scores on the FSS and COF subscales, meaning fatigue had a greater impact on their lifestyle. On the HADS, patients with TBI were more anxious ($p=0.04$) and depressed ($p<0.001$) than controls. In the TBI group, 43% had clinically significant anxiety and 40% had clinically significant depression.

	(COF), Hospital Anxiety and Depression Scale (HADS).	3. 64% of patients with TBI had clinically significant fatigue (FSS<4) versus 35.1% of controls.
Englander et al. (2010) USA Observational N=119	Population: TBI=119; Mean Age=40yr; Gender: Male=80, Female=39; Mean Time Since Injury=9yr. Intervention: Participants completed a survey and had blood tests done looking at growth hormone reserves. Outcome Measure: Global Fatigue Index (GFI), Multidimensional assessment of fatigue (MAF), Craig Handicap Assessment and Reporting Technique (CHART), Neurobehavioral Functioning Inventory (NFI), Fatigue severity scale (FSS), Pittsburgh sleep quality index (PSQI), Pain.	1. Using the PSQI, more than two-thirds of patients with TBI had abnormal sleep; one-third had abnormal sleep based on the FSS. 2. Pain intensity was positively correlated with depression and sleep problems (both $p<0.0001$). Depression and sleep problems also correlated ($p<0.0001$). 3. MAF-Activities of Daily Living fatigue subscale correlated with female gender, depression and lower CHART social scores. 4. Depression ($p<0.002$), pain intensity ($p<0.006$) and NFI motor deficits ($p<0.007$) were significant predictors of fatigue (GFI). 5. Depression and NFI motor deficits were predictors of abnormal fatigue on the FSS ($p<0.01$). 6. Pituitary dysfunction did not correlate with fatigue.
Ashman et al. (2008) USA Case-Control N=275	Population: TBI=202, Healthy controls=73. <i>TBI Group:</i> Mean age=47.7yr; Gender: Male=109, Female=93; Mean Time Post Injury=14.7yr. <i>Control Group:</i> Mean age=41.7yr; Gender: Male=28, Female=45. Intervention: Administered a 30-minute computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) at 3 time points (baseline, immediately after the first baseline assessment, and 2hr later). Measures of fatigue were obtained at the start and end of testing. Outcome Measure: CANTAB, Global Fatigue Index, and situational fatigue rating.	1. There was a significant difference between groups on the rating of day to day fatigue and situational fatigue ($p<0.001$), with the TBI group having higher rates. 2. There was a significant time by group interaction ($p<0.04$); the control group improved between 1 st and 2 nd test but the TBI group performance did not significantly change between time points. 3. Accuracy differed significantly between time points ($p<0.04$). The control group remained stable but the TBI group declined between the 2 nd and 3 rd time points. 4. For the TBI group, higher levels of subjective fatigue were associated with response speed.
Bushnik et al. (2008) USA Case Series N=51	Population: TBI=51; Mean age=31yr; Gender: Male=39, Female=12. Intervention: After discharge, fatigue was assessed at various time points: enrollment (baseline) and 3, 6, 12, 18, and 24mo post TBI. Outcome Measure: Barroso Fatigue Scale (BFS), Fatigue Severity Scale (FSS), Global Fatigue Index (GFI), Beck Depression Inventory-II, Craig Handicap Assessment Reporting Technique, Neurobehavioral Functioning Inventory (NFI), Pittsburgh Sleep Quality Index (PSQI), Visual Analogue Scale-Pain (VAS).	1. GFI scores decreased from T1 (2.6mo post injury) to T2 (12.6mo) (23 to 17, $p=0.0018$). There were no significant changes seen on the Barroso subscales or the FSS. 2. Decreases over time were also noted for the VAS ($p<0.0001$), the PSQI ($p<0.01$) and the NFI motor subscale ($p<0.01$). 3. Increases over time were significant for the CHART Cognitive Independence ($p<0.0001$) and occupation subscales ($p<0.001$). 4. The GFI increase group had higher PSQI scores than the GFI same and GFI decrease groups ($p<0.01$).
Ziino & Ponsford (2006a) Australia Case-Control N=92	Population: TBI=46, Healthy controls=46. <i>TBI Group:</i> Mean age=35.28yr; Mean Time Post Injury=240.3d; Mean GCS=10. <i>Control Group:</i> Mean age=34.07yr. Intervention: Patients completed a 45-minute vigilance task and the Complex	1. Groups differed significantly on the FSS ($p=0.017$) with fatigue having a greater impact on the lifestyle of those with TBI. 2. Based on the HADS (score >7), more individuals in the TBI group were

	<p>Selective Attention Task (C-SAT). Outcome Measure: Causes of Fatigue Questionnaire (COF), Visual Analogue Scale –Fatigue (VAS-F), Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS).</p>	<p>depressed than in the control group (39.1% vs 6.5%, $p<0.001$).</p> <ol style="list-style-type: none"> Higher depression scores in the TBI group were associated with greater fatigue, lower vigour and higher scores on the COF-Mental effort subscale ($p<0.01$). In the TBI group, anxiety scores were associated with greater fatigue (VAS-F and FSS), lower vigour and greater COF scores (physical and mental subscales $p\leq 0.05$).
<p>Borgaro et al. (2005) USA Case-Control N=77</p>	<p>Population: TBI=47, Healthy Controls=30. <i>TBI Group:</i> Mean Age=35.93yr; Gender: Male=26, Female=21; Mean GCS=9.39; Mean Time Post Injury=24.37d. <i>Control Group:</i> Mean Age=36.2yr; Gender: Male=19, Female=11. Intervention: Fatigue assessment completed within 90d of injury. Outcome Measure: Barrow Neurological Institute (BNI) Fatigue Scale, BNI screen for higher cerebral functions (BNIS).</p>	<ol style="list-style-type: none"> Based on the BNI fatigue scale, those with TBI had higher levels of fatigue than those in the control group ($p=0.002$). Self-reports of fatigue did not appear to be influenced by cognitive performance, days since injury, injury severity or gender. Scores of the BNIS indicated that those with severe injuries had greater cognitive impairment than those with moderate and mild injuries ($p<0.004$).
<p>LaChapelle & Finlayson (1998) Canada Case-Control N=60</p>	<p>Population: TBI=24, ABI=5, Stroke=1; Healthy Controls=30. <i>Experimental Group (TBI, ABI, stroke; n=30):</i> Mean age=31.9yr; Gender: Male=22, Female=8; Mean Time Post Injury=44.3mo. <i>Control Group (n=30):</i> Mean Age=31.9yr. Intervention: Participants completed a survey and a thumb press exercise (4 trials). Outcome Measure: Visual Analogue Scale for Fatigue (VAS-F), Fatigue Severity Scale (FSS), Fatigue Impact Scale (FIS), Objective measurement of fatigue (thumb pressing).</p>	<ol style="list-style-type: none"> There were significant between group differences on the FSS ($p<0.001$), vigour subscale of the VAS-F ($p<0.01$) and a subscale of the FIS (fatigue on cognitive, physical and social functioning $p<0.001$), with the TBI group displaying greater levels of fatigue. Results from the objective measure of fatigue indicated that participants with TBI fatigued more quickly than non-TBI participants. Scores on the VAS-F fatigue subscale were not statistically different between groups.

Discussion

When comparing individuals with TBI to healthy controls, it is apparent that those who sustained a brain injury report greater levels of fatigue (Ashman et al. 2008; Borgaro et al. 2005; Chiou et al. 2016; LaChapelle & Finlayson 1998; Ponsford et al. 2012; Ziino & Ponsford 2006a). Between 33% and 64% of individuals reported fatigue post TBI (Englander et al. 2010; Ponsford et al. 2012). Englander et al. (2010) found that over two-thirds of participants ($n=119$) had abnormal sleep based on the Pittsburgh Sleep Quality Index. The overwhelming conclusion is that fatigue has a greater impact on the lifestyles of those with brain injuries.

Bushnik et al. (2008) found improvements on self-reported fatigue during the first year post injury, although no further changes were seen up to two years post TBI. Unfortunately, when fatigue worsened over the course of two years, it was accompanied by poorer cognitive and motor outcomes as well as reduced levels of general functioning (Bushnik et al. 2008). The former conclusions are unfortunate as the literature suggests that pain, depression and motor deficits are significant predictors of fatigue post TBI (Englander et al. 2010), which could perpetuate a cycle of disability if fatigue is not appropriately managed. The studies have also shown pain, depression and anxiety to be associated with fatigue (Englander et al. 2010; Ponsford et al. 2012; Ziino & Ponsford 2006a). Furthermore, it is problematic given individuals are less aware of the effect of fatigue on their lifestyles (Chiou et al. 2016). Chiou et al.

(2016) found that reduced awareness of fatigue in the physical and psychosocial domain is associated with anxiety, whereas reduced awareness in the physical and cognitive domain is associated with depression. Disability has also been correlated with fatigue (Juenst et al. 2013). Again, fatigue proves to be a complex and multifaceted concept.

Conclusions

There is level 3 evidence that those who sustain a TBI report greater levels of fatigue post injury.

Fatigue symptoms appear to be increased in individuals who sustain an ABI.

15.2.1 Impact of Fatigue on Participation and Quality of Life Post ABI

There are many challenges to studying fatigue post TBI. One of the challenges is in separating fatigue from pain, depression and many other health related issues. Several assessments, including the DSM-IV (American Psychiatric Association) and the Beck Depression Inventory (Beck et al. 1996), assess fatigue as a symptom of depression. Few scales assess fatigue alone. To do so, one must reduce the overlap that exists between the various scales or tools that are used post TBI (Cantor et al. 2008). This section describes the impact that fatigue has on an individual's life post injury.

Individual Study

Table 15.3: Fatigue and its Impact on Participation and Quality of Life

Author/Year Country/Study Design	Methods	Outcome
Ponsford et al. (2015) Australia Observational N=72	Population: TBI; Mean Age=30yr; Gender: Male=56, Female=16; Mean Time Post Injury=305d; Mean GCS=8. Intervention: Participants completed a series of assessments to determine the relationship between fatigue and vigilance, depression and anxiety post-TBI. Outcome Measure: Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS), Vigilance task.	<ol style="list-style-type: none"> 1. Association between vigilance performance and fatigue according to FSS was not significant ($p>0.05$). 2. Fatigue strongly predicted depression and anxiety according to HADS and daytime sleepiness according to ESS ($p<0.05$). 3. Depression significantly predicted daytime sleepiness and anxiety ($p<0.05$). 4. Error rate on vigilance task was predicted by depression ($p<0.05$), but not anxiety ($p>0.05$).
Esbjornsson et al. (2013) Sweden Observational N=18	Population: TBI=18; Age Range=19-62yr; Gender: Male=9, Female=9; Median GCS=9.5. Intervention: Participants completed questionnaires 1yr post injury. Outcome Measure: Daily Fatigue Impact Scale (D-FIS), Barrow Neurological Institute Screen for Higher Cerebral Functions, European Questionnaire 5 Dimensions Health-related Quality of Life, European Brain Injury Questionnaire (EBIQ).	<ol style="list-style-type: none"> 1. D-FIS and EBIQ scores correlated significantly ($p=0.004$). Fatigue was associated with subjective determination of cognitive problems ($p<0.001$). 2. Using the EBIQ, fatigue was associated with feeling tired ($p<0.001$), difficulties in decision making ($p=0.004$), difficulty getting things done on time ($p<0.001$) and working slowly for accuracy ($p<0.001$). 3. Fatigue caused individuals to react too quickly to others ($p<0.001$).

<p>Huang et al. (2013) USA Case Series N=48</p>	<p>Population: TBI=48; Mean Age=30.7yr; Gender: Male=37, Female=11; Severity: Mild=15, Moderate=7, Severe=26. Intervention: Data obtained from medical charts and questionnaires completed at 6 and 12mo follow-up. Outcome Measure: Beck Depression Inventory (BDI), Neurobehavioral Functional Inventory (NFI), Impact Event Scale (IES).</p>	<ol style="list-style-type: none"> 77% of participants had sleep complaints post injury. 25 had persistent sleep complaints (PSC; present at 6 or 12mo) and 23 did not. Those with PSC, compared to those without, had higher scores on the BDI (15.8 versus 6.7, $p=0.001$) and IES (19.6 versus 9.4, $p=0.03$) at 12mo. No significant differences were found for the NFI.
<p>Schnieders et al. (2012) Netherlands Observational N=90</p>	<p>Population: TBI=90; Mean age=37yr; Gender: Male=64, Female=26; Severity: Moderate=25, Severe=65. Intervention: Participants completed questionnaires and endocrine testing. Two groups were created; those with fatigue ($n=48$) and those without ($n=42$). Outcome Measure: Pittsburgh Sleep Questionnaire (PSQ), Epworth Sleepiness Scale (ESS), Quality of Life in Brain Injury (QoLiBri), Assessment of Growth Hormone Deficiency in Adults (AGHDA), Hospital Anxiety and Depression Scale (HADS).</p>	<ol style="list-style-type: none"> The fatigue group, compared the group without fatigue, had more females ($p=0.05$), used more medications, especially antiepileptics ($p=0.01$), had lower job levels ($p<0.01$) and more nonpaying jobs ($p<0.05$). Compared to patients without fatigue, those with fatigue scored significantly lower on sleep quality (PSQ), and demonstrated more daytime sleepiness (ESS), anxiety and depression (HADS), as well as lower quality of life (QoLiBri and AGHDA; $p<0.001$ for all). Vitamin D deficiency was more common in those with fatigue compared with those without (81% versus 45%, $p<0.001$).
<p>Fogelberg et al. (2012) USA Case-Control N=181</p>	<p>Population: TBI=129; Healthy Controls=52. <i>TBI Group:</i> Mean Age=37.1yr; Gender: Male=100, Female=29; Mean GCS=9.3. <i>Healthy Controls:</i> Mean Age=59.9yr; Gender: Male=40, Female=12. Intervention: Questionnaires completed 1yr post injury. Outcome Measure: Pittsburgh Sleep Quality Index (PSQI), Functional Independence Measure (FIM), Disability Rating Scale (DRS), Satisfaction With Life Scale (SWLS).</p>	<ol style="list-style-type: none"> 44% ($n=129$) of participants with TBI had clinically significant sleep disturbance at 1yr (PSQI >5). Those with sleep disturbance, compared to those without, had significantly worse scores on the FIM, DRS, and SWLS ($p<0.001$). Compared to healthy controls, participants with TBI took longer to fall asleep (sleep latency), used more sleep medications, had more daytime dysfunction, lower sleep quality, and a worse overall global score (all $p<0.001$).
<p>Bay & de-Leon (2011) USA Observational N=84</p>	<p>Population: TBI=84; Mean Age=38.0yrs; Gender: Male=43, Female=41; Mean Time Since Injury=14.9mo; Injury Severity: Mild=41, Moderate=43. Intervention: Individuals from an outpatient clinic completed a self-report survey. Medical history was obtained from the patient charts. Outcome Measure: Perceived Stress Scale (PSS), Impact of Events Scale (IES), Neurobehavioural Functioning Inventory (NFI), Fatigue Related Quality of Life (QOL-F).</p>	<ol style="list-style-type: none"> 27% of patients reported no present level of fatigue. NFI-S was significantly associated with the PSS ($p=0.002$) and the IES ($p=0.000$). Gender and TBI severity were associated with IES. Specifically females ($p=0.032$) and individuals with mild injuries ($p=0.006$) had higher IES scores. For individuals living in the community, the QOL-F was significantly associated with somatic symptoms of TBI (NFI; $p<0.001$) and situational stress (PSS; $p=0.011$).
<p>Cantor et al. (2008) USA Case-Control N=308</p>	<p>Population: TBI=223, Controls=85; Gender: Male=151, Female=157. <i>TBI Group:</i> Mean age=47.8yr; Mean Time Post Injury=15yr; Severity: Mild=64, Moderate/Severe=105. <i>Control Group:</i> Mean age=43yr.</p>	<ol style="list-style-type: none"> 75% and 40% of participants in the TBI and control groups respectively had significant fatigue (GFI score >21; $p<0.001$). For the control group, fatigue was negatively correlated with income ($r=-0.304$, $p=0.007$).

	<p>Intervention: Participants completed outcome measures via an interview and survey.</p> <p>Outcome Measure: Global Fatigue Index (GFI), Beck Depression Inventory, McGill Pain Questionnaire, Pittsburgh Sleep Questionnaire, Participation Objective Participation Subjective, SF-36-Health Survey, Life-3.</p>	<ol style="list-style-type: none"> 3. In both groups, GFI scores were significantly higher among women than men (TBI group, $p=0.010$; Control, $p=0.019$). 4. The TBI group, compared to controls, had greater levels of fatigue ($p<0.001$), depression ($p<0.001$), pain ($p<0.05$), poorer sleep quality ($p=0.003$) and poorer health related quality of life ($p<0.05$). 5. Overall quality of life did not differ significantly between groups ($p=0.069$). 6. For both groups, fatigue was significantly negatively correlated with all aspects of health-related quality of life ($p<0.05$). For the TBI group, fatigue was significantly correlated with overall quality of life ($p<0.001$).
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Discussion

Unfortunately Individuals with TBI were shown to not only use more sleep medications but also have longer sleep latency, lower sleep quality and more daytime dysfunction compared to healthy controls (Fogelberg et al. 2012). Further, those in the TBI group showed greater levels of fatigue, depression, and pain and reported poorer health related quality of life (Cantor et al. 2008). Even when compared to a group of patients with TBI, Schnieders et al. (2012) found that those with fatigue had more anxiety and depression as well as lower quality of life. Ponsford et al. (2015) also discovered that fatigue predicts anxiety and depression, and that depression may predict excessive daytime sleepiness. Huang et al. (2013) found those with persistent sleep complaints had higher scores on the beck depression inventory and the impact event scale. It is through these studies that it becomes apparent how many facets of life are impacted by sleep disturbances and fatigue.

Sleep disturbances were shown to negatively impact ones satisfaction with life, and scores on the Functional Independence Measure and Disability Rating Scale (Fogelberg et al. 2012). Moreover, fatigue has been associated with subjective determination of cognitive problems, difficulties with decision-making, working slowly to ensure accuracy and challenges in getting things done on time (Esbjörnsson et al. 2013). Fatigue can also negatively impact upon relationships, as there is a tendency towards reacting too quickly in response to others among individuals suffering from fatigue (Esbjörnsson et al. 2013). Further, one's ability to work is often compromised when sleep disturbances are present. Schnieders et al. (2012) found those with fatigue, compared to those without, had lower level jobs and more nonpaying jobs. Evidently, managing fatigue is imperative in helping individuals live a productive and quality life post injury.

Conclusion

There is Level 3 evidence to suggest that higher levels of fatigue may lead to a poorer quality of life.

Higher levels of fatigue lead to a poorer quality of life.

Fatigue and sleep disturbances impact individuals physically, cognitively, and psychologically.

Individuals with fatigue and sleep disturbances may have increased levels of anxiety and depression.

Those with fatigue, compared to those without, were shown to have lower level jobs and more nonpaying jobs.

Fatigue related quality of life is associated with somatic symptoms of TBI and situational stress.

15.2.2 Vigilance and Fatigue

Vigilance has been defined as the ability to sustain a level of alertness over long periods of time (Parasuraman 1984). It has been noted that those who sustain a TBI do have a lower cognitive reserve and often are not able to maintain the same levels of vigilance or sustained attention as they did before the injury (Ziino & Ponsford 2006b). It has been suggested that this variability in performance may be the result of fatigue (Cohen 1993).

Individual Study

Table 15.4: Vigilance and Fatigue Post TBI

Author/Year Country/Study Design	Methods	Outcome
Ponsford et al. (2015) Australia Observational N=72	Population: TBI; Mean Age=30yr; Gender: Male=56, Female=16; Mean Time Post Injury=305d; Mean GCS=8. Treatment: Participants completed a series of assessments to determine the relationship between fatigue and vigilance, depression and anxiety post-TBI. Outcome Measure: Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS), Vigilance task.	<ol style="list-style-type: none"> 1. Association between vigilance performance and fatigue according to FSS was not significant ($p>.05$). 2. Fatigue strongly predicted depression and anxiety according to HADS and daytime sleepiness according to ESS ($p<.05$). 3. Depression significantly predicted daytime sleepiness and anxiety ($p<.05$). 4. Error rate on vigilance task was predicted by depression ($p<.05$), but not anxiety ($p>.05$).
Ziino & Ponsford (2006b) Australia Case-Control N=92	Population: TBI=46, Healthy Controls=46; <i>TBI Group:</i> Gender: Male=29, Female=17; Mean Age=35.28yr; Mean Time Post Injury=240.3d; Mean GCS=10. <i>Control Group:</i> Gender: Male=28, Female=18; Mean age=34.07yr. Intervention: Participants completed a 45-minute vigilance task and the Complex Selective Attention Task. Outcome Measure: Causes of Fatigue Questionnaire, Visual Analogue Scale – Fatigue (VAS-F), Fatigue Impact Scale, Fatigue Severity Scale.	<ol style="list-style-type: none"> 1. When comparing the two groups, results indicated: 1) decision-making on the vigilance task was significantly slower ($p<0.001$) for the TBI group, 2) decision-making became faster for controls ($p=0.006$) but not for the TBI group ($p=0.52$), and 3) the TBI group had a slower movement speed ($p<0.001$). 2. The TBI group had higher pre-vigilance VAS-F fatigue ratings and these were associated with more missed targets over the entire vigilance task ($p<0.03$).

Discussion

In the study conducted by Ziino and Ponsford (2006b), individuals with TBI demonstrated slower decision-making on the vigilance task than those without TBI ($p<0.001$). Despite decision-making

becoming faster for controls, this was not the case for the TBI group. The movement speed was also slower for those with TBI than for controls ($p < 0.001$). Results from the fatigue subscale indicate that both groups had increased fatigue levels following the completion of the vigilance tasks. Therefore, although participants with TBI performed at a lower level on the task, the level at which they performed was consistent during the vigilance task. Those in the TBI group also had higher diastolic blood pressure readings afterwards, which were associated with subjective fatigue levels. Ziino and Ponsford (2006b) suggest that, in order to maintain a stable level of performance, individuals with TBI are forced to expend more energy (psychologically, physiologically, etc.) and this is associated with subjectively increased levels of fatigue.

When the relationship between fatigue and vigilance was analyzed, Ponsford et al. (2015) discovered that there is a trend that decreased vigilance is associated with increased fatigue, but this relationship did not reach statistical significance. However, Ponsford et al. (2015) found that fatigue may predict and contribute to the onset of depression, anxiety, and daytime sleepiness. Depression in turn can predict decreased vigilance and is associated with anxiety and daytime sleepiness (Ponsford et al. 2015). Unfortunately, this multifaceted perpetuating cycle renders the study and treatment of fatigue complex. Ponsford et al. (2015) suggest a treatment approach that aims to alleviate fatigue could be to target these individual factors.

Conclusions

There is Level 3 evidence, based on one study, that individuals who sustain a TBI do experience greater levels of fatigue and a decrease in vigilance, compared to those without an injury.

Fatigue experienced post-TBI has been linked to a decrease in vigilance.

Within TBI population, the relationship between vigilance and fatigue is affected and confounded by depression, anxiety, and sleep disturbances.

15.3 Non-pharmacological Management Strategies

Fatigue post ABI can be managed using pharmacological or non-pharmacological techniques. Non-pharmacological strategies include educating both patients and their family members about the occurrence of fatigue post TBI and how to manage expectations. Diet and lifestyle may also play a role in combating fatigue; thus it is believed that eating a “balanced diet” and learning to balance exercise with rest may help to reduce fatigue (Elovic et al. 2005; Rao et al. 2006).

15.3.1 Pacing

Those who are suffering from fatigue may benefit by performing important activities when they feel they are at their best (Lezak 1978). Conserving energy and pacing are two ways an individual is encouraged to overcome or deal with his or her levels of fatigue following brain injury (Fellus & Elovic 2007). Many patients find that simple tasks require more concentration and effort than they did previously and, as a result, they tire more easily (Lezak 1978). As part of their rehabilitation, individuals may be taught or re-taught how to prioritize their commitments and are encouraged to recognize their abilities and limitations (Fellus & Elovic 2007). For some this may come easily, but for others it may require more education or other interventional programs (Fellus & Elovic 2007). Although pacing is a

concept that has been accepted with health care professionals and encouraged within the ABI/TBI population, its benefits have not yet been studied with this group.

The effects of pacing strategies for those who have sustained an ABI are not known.

15.3.2 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) has been found to be effective at improving fatigue in disorders such as multiple sclerosis, chronic fatigue syndrome, and rheumatoid arthritis (Cantor et al. 2014). However limited research exists on the effect of fatigue and sleep disturbances after brain injury (Ouellet & Morin 2004). Sleep disorders, such as insomnia, can affect a person's quality of life, family and social commitments, as well as their ability to return to work (Ouellet & Morin 2004). CBT for the treatment of insomnia among a brain injury population was studied in a single study.

Individual Study

Table 15.5: Cognitive Behavioural Therapy for the Treatment of Insomnia

Author/Year Country/Study Design	Methods	Outcome
<p>Ouellet & Morin (2007) Canada Pre-Post N=11</p>	<p>Population: TBI=11; Mean age=27.3yr; Male=6, Female=5; Mean Time Since Injury=25.64mo.</p> <p>Intervention: Two nights of polysomnographic evaluation in a sleep lab and a diagnostic interview for insomnia. 8x1hr weekly sessions of cognitive behavioural therapy (CBT) for insomnia were then provided.</p> <p>Outcome Measure: Sleep Diary, Insomnia Severity Index (ISI), Multidimensional Fatigue Inventory (MFI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS).</p>	<ol style="list-style-type: none"> Following CBT, significant improvements were seen in total wake time ($p<0.001$) and sleep efficiency ($p=0.01$). Gains were maintained, but no significant changes occurred from the post treatment assessment and 3mo follow-up for total wake time ($p=0.06$) or sleep efficiency ($p=0.24$). Sleep time from pre to post treatment did not change significantly ($p=0.44$); however, there was a significant difference from baseline to the 3mo follow-up ($p<0.015$). Significant reductions in scores were seen after treatment on the DBAS, ISI (both $p<0.01$), and the MFI ($p<0.012$).

Discussion

Ouellet and Morin (2007) found that CBT was effective in dealing with insomnia. Patients received eight to ten weeks of CBT, totaling eight sessions. For some, improvements in sleep were noted within the first 2 weeks of treatment; for others, improvement was more progressive. Pre to post treatment, significant improvements were found for total wake time ($p<0.001$), sleep efficacy ($p=0.01$), fatigue ($p<0.012$), and insomnia ($p<0.01$) but not for total sleep time (Ouellet & Morin 2007). No additional significant gains were made once the treatment had concluded, although gains were maintained at 3-month follow-up. This study suggests that a relatively short duration of CBT can lead to positive sleep improvements. Evidently, psychological interventions for insomnia may have therapeutic benefits for individuals post TBI.

Conclusion

There is Level 4 evidence, based on one study, to suggest that cognitive behavioural therapy may assist in treating insomnia and help in the management of fatigue post TBI.

Cognitive behavioural therapy has been shown to be effective in treating insomnia related to TBI. Additional research in this area is warranted.

15.3.3 Acupuncture

The use of acupuncture has been shown to be of benefit in treating insomnia within healthy individuals and other patient populations; however, the research is limited within a brain injury population.

Table 15.6 Acupuncture as a Treatment for Insomnia Post ABI

Author/Year Country/Study Design	Methods	Outcome
Zollman et al. (2012) USA RCT PEDro=5 N _{Initial} =24, N _{Final} =20	<p>Population: TBI=20; Male=9, Female=11. <i>Treatment Group (n=12):</i> Mean age=44.5yr; Mean Time Since Injury=2.17yr. <i>Control Group (n=8):</i> Mean age=43.5yr; Mean Time Since Injury=3yr.</p> <p>Intervention: Actigraph worn for 72hr before and after treatment. Treatment group received acupuncture treatments (20min sessions) and the control received only instructions on good sleep habits.</p> <p>Outcome Measure: The Insomnia Severity Index (ISI), Hamilton Depression Rating Scale, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Test (PASAT).</p>	<ol style="list-style-type: none"> ISI scores did not differ significantly between groups at baseline ($p=0.47$), post treatment ($p=0.14$) or at 1mo follow-up ($p=0.08$). The treatment group showed decreased ISI scores from baseline to post treatment ($p<0.01$) and from baseline to 1mo follow-up ($p<0.01$); no significant differences were found in the control group. Baseline depression was positively associated with ISI scores at baseline ($p<0.01$) but not post treatment ($p=0.45$). PASAT scores were positively associated with ISI at baseline ($p=0.02$) and follow-up ($p=0.03$). RBANS scores were not associated with sleep variables.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al. 2002)

Discussion

Zollman et al. (2012) explored the use of acupuncture, compared to education, in addressing issues of insomnia within a TBI population. A between group comparison showed no significant difference in the Insomnia Severity Index (ISI) scores at three time points (e.g., baseline, post treatment and at one month post treatment). The groups also did not differ significantly in terms of sleep time pre and post treatment. When examining the within-group ISI scores, the treatment group showed a statistically significant decrease in the perception of insomnia severity between pre and post treatment. No such differences were seen in the control group. Those in the treatment group also showed significant improvement on overall cognitive functioning and divided attention. This treatment modality should be studied further within a brain injury population

Conclusions

There is Level 2 evidence to suggest acupuncture is effective in improving perception of sleep and sleep quality in those who sustain a TBI.

Acupuncture therapy has been shown to improve perception of sleep and sleep quality; however due to the small sample further research is needed.

15.3.4 Light Therapy

Light therapy has not been well studied in the ABI population; however, it has been said to be a potential treatment modality to address fatigue and daytime sleepiness. In healthy individuals and other patient populations, light exposure has led to improvements in sleepiness, mood and vigilance performance, as well as resulted in an arousing effect on various biological mechanisms (Ponsford et al. 2012).

Table 15.7: Light Therapy as a Treatment for Sleep

Author/Year Country/Study Design	Methods	Outcome
Sinclair et al. (2014) Australia RCT PEDro=6 N=30	<p>Population: TBI=30; Mean Age=42yr; Male=24, Female=6; Mean Time Since Injury=1106d; Severity: Mild=7, Moderate=8, Severe=15.</p> <p>Intervention: Participants were randomized to one of three groups: blue light therapy (n=10), yellow light therapy (n=10) or the no treatment control group (n=10). Sessions were 45min daily for 4wk.</p> <p>Outcome Measure: Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI).</p>	<ol style="list-style-type: none"> 1. Compared to controls, the blue light therapy group showed a significantly greater reduction in fatigue (FSS; $p<0.001$) and a significant reduction in daytime sleepiness (ESS; $p<0.01$). However, these improvements were not observed in the yellow light therapy group when compared to controls. 2. There was no significant change in PSQI score in any treatment condition ($p>0.05$).

Discussion

Sinclair et al. (2014) conducted a RCT examining the effectiveness of light therapy, both blue and yellow, compared to a control group. The blue light therapy was shown to significantly decrease fatigue ($p<0.001$) and daytime sleepiness ($p<0.01$) compared to the control group. The yellow light therapy did not show such improvements compared to the control group. The improvements measured during the treatment phase did not persist at follow-up (week 8).

Conclusion

There is level 1b evidence, from a single study, that blue light therapy is effective in reducing fatigue and daytime sleepiness during treatment.

Blue light therapy was found to reduce fatigue and daytime sleepiness; however the improvements did not persist beyond the treatment period.

15.4 Pharmacological Management Strategies

Individuals who have sustained a brain injury often have cognitive disabilities as a result. Insomnia and sleep disorders have been known to compound the neurocognitive difficulties experienced post injury. Despite the knowledge that fatigue and sleep disorders play a role in the recovery from an ABI very few interventions have been developed to help manage these issues. Many pharmacological interventions have been tested in other populations (narcolepsy, multiple sclerosis, Parkinson's, etc.) (Rao et al. 2006), but few have been tested within the ABI population specifically. Treatments have included the administration of various over-the-counter medications (e.g., Sleep-Eze, Nytol, etc.) (Thaxton & Patel 2007). There has been some discussion about the possible therapeutic benefits of using medications such as methylphenidate, dextroamphetamine, carbidopa, amantadine, and modafinil to treat fatigue post TBI (Rao et al. 2006).

15.4.1 Modafinil

Modafinil, a wakefulness promoting agent, was approved to address EDS (Jha et al. 2008). Additionally, the drug was approved for use to address narcolepsy and sleeping difficulties associated with shift work ("Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group" 2000; "Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group" 1998). Modafinil was found to enhance the quality of life for those with narcolepsy (Beusterien et al. 1999). Studies exploring modafinil for fatigue and EDS among Parkinson's disease, multiple sclerosis, TBI, and post-polio syndrome populations provide inconsistent results (Sheng et al. 2013). Studies exploring the effectiveness of Modafinil within the ABI population are limited.

Individual Study

Table 15.8: Modafinil Treatment for Fatigue Post ABI

Author/Year Country/Study Design/PEDro Score	Methods	Outcome
Kaiser et al. (2010) Switzerland RCT PEDro=9 N=20	<p>Population: TBI=20; Gender: Male=17, Female=3. <i>Treatment Group (n=10):</i> Mean age=37yr; Mean GCS=7. <i>Control Group (n=10):</i> Mean age=43yr; Mean GCS=8.</p> <p>Intervention: Actigraphy and nocturnal polysomnography at baseline. Patients received either modafinil (100mg 1x/d then 2x/d) or placebo for 6wk.</p> <p>Outcome Measure: Excessive Daytime Sleepiness (EDS), Fatigue Severity Scale (FSS), Maintenance of wakefulness test (MWT).</p>	<ol style="list-style-type: none"> At 6 weeks, the decrease in FSS scores was greater in the modafinil group (-0.8± 1.0 versus 0.0± 0.6), but this was not significant (p=0.07). The modafinil group had greater decreases in EDS scores versus placebo (p<0.005). On the MWT, a significant increase was shown for the modafinil group when compared to placebo (8.4± 9.6 versus 0.4± 6.2min, p=0.04). Of those patients with fatigue at baseline (FSS≥4), decreases in FSS scores were not greater in the treatment group.
Jha et al. (2008) USA RCT PEDro=8 N _{Initial} =51, N _{Final} =46	<p>Population: TBI=51; Mean age=38.25yr; Gender: Male=35, Female=16; Mean Time Post Injury=5.77yr.</p> <p>Intervention: Treatment group (n=27) received modafinil (100mg 1x/d for 3d, then 2x/d for 11d). A maintenance dose of 100mg was given 2x/d. The control group (n=24) received a placebo. At the</p>	<ol style="list-style-type: none"> No significant between group differences were found at week 4 or week 10 on the FSS (p=0.80 and p=0.61, respectively) or the MFI (p=0.67 and p=0.73, respectively). The change in ESS scores was significantly greater in the modafinil group versus placebo at week 4 (p=0.02) but not at week 10 (p=0.56).

	end of phase 1 (8wk) both groups crossed-over. Outcome Measure: Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFI), Epworth Sleepiness Scale (ESS).	3. Adverse events for treatment included: headaches (29.5%), insomnia (19.6%), fatigue (9.8%), dizziness (7.8%) and tremors (5.9%). 4. Adverse events reported for placebo: headaches.
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PE德罗=Physiotherapy Evidence Database rating scale score (Moseley et al. 2002).

Discussion

Two RCTs examined the effects of modafinil on fatigue and EDS for individuals with TBI (Jha et al. 2008; Kempf et al. 2010). The two studies followed similar protocols with the initial administration of modafinil 100mg daily, which was then titrated up to 100mg twice per day, and both compared with a placebo control group. Both studies found no significant difference in fatigue, as measured by the FSS, between the treatment and control groups. Further, when Kaiser et al. (2010) compared those with fatigue at baseline (FSS ≥ 4) in both groups, the decrease in FSS scores remained non-significant between groups. The two studies also examined EDS using the Epworth Sleepiness Scale. The treatment groups both showed a significantly greater decrease in Epworth Sleepiness Scale scores when compared with controls, representing a greater improvement in EDS (Jha et al. 2008; Kempf et al. 2010). It should be noted, however, that Jha et al. (2008) found the improvement to be significant at week four ($p=0.02$) but not at week ten ($p=0.56$), highlighting that there was no clear temporal pattern of benefit. Of concern, those receiving modafinil reported more insomnia than controls ($p=0.03$) (Jha et al. 2008). These studies suggest that modafinil may not be effective for improving fatigue.

Conclusion

There is Level 1a evidence that Modafinil is not effective in treating fatigue but has been shown to be effective short-term in treating excessive daytime sleepiness post ABI.

Modafinil has not been shown to be effective in treating fatigue.

Modafinil has been shown to be effective short-term in treating excessive daytime sleepiness, but may also cause insomnia.

15.4.2 Methylphenidate

Of the neurostimulants used in the post-acute care of TBI, methylphenidate is common, assisting with memory, attention, verbal fluency, and improving processing speed. While its use is heavily focused on the improvement of functional and cognitive deficits, methylphenidate has been reported to have unfavourable effects on sleep patterns post brain injury. Little research has focused directly on the effects of methylphenidate on the sleep-wake cycles of those with ABI (Al-Adawi et al. 2006).

Individual Study

Table 15.9: Methylphenidate Treatment for Sleep Disorders

Author/Year Country/Study Design	Methods	Outcome
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<p>Al-Adawi et al. (2006) Oman Case-Control N=30</p>	<p>Population: TBI=30; Mean age=51yr; Gender: Male=23, Female=7. Intervention: This study was retrospective in nature. Patients receiving methylphenidate (5-10mg at 8am and 2pm) made up the treatment group (n=17). The control group (n=13) were patients that received no medication. Outcome Measure: Sleep State, Functional Independence Measure (FIM), Rancho Los Amigo Levels of Cognitive Functioning.</p>	<ol style="list-style-type: none"> 1. The mean hours of sleep during a 24-hr period did not significantly differ between the treatment and control group (8.3 versus 9.0hr, p=0.096). 2. Mean hours of sleep at night for the treatment and control groups were 6.4 and 6.9hrs, respectively. 3. Mean total FIM score at baseline was lower for those in the methylphenidate group than for controls (30.0 versus 34.9, p=0.4). 4. Rancho Scale scores were comparable between groups at baseline (p=0.479).
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Discussion

In a double-blind, placebo-controlled study looking at the effects of methylphenidate, sertraline or placebo on individuals with a mild or moderate TBI, Lee et al. (2005) noted that those on methylphenidate, along with those in the placebo group, reported significantly less daytime sleepiness than those in the sertraline group. In this study, all medications were given during the day for a total of four weeks, which may have impacted on the effectiveness of sertraline (Lee et al. 2005). In the study by Al-Adawi et al. (2006) no significant differences were found between those who received methylphenidate and those who did not when looking at the scores of various assessment scales (e.g., activities of daily living, mobility and cognition). More importantly, sleep times between the two groups were not significantly different. Based on this study, methylphenidate does not seem to have adverse effects on the sleep-wake cycle.

Conclusion

There is Level 3 evidence, based on a single study, that methylphenidate does not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI.

Methylphenidate does not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI when given in commonly accepted dosages.

15.4.3 Lorazepam and Zopiclone

Lorazepam, a benzodiazepine also known as Ativan or Temesta, is primarily an anti-anxiety medication that due to its side effects has been used for the treatment of sleep disorders (Thaxton & Patel 2007). Zopiclone is a non-benzodiazepine medication, however it works at the same receptor sites as benzodiazepines. Zopiclone has been used in the treatment of insomnia for individuals experiencing problems with delayed sleep onset, difficulties maintaining sleep, and/or early waking (Hair et al. 2008; Thaxton & Patel 2007). In a randomized, crossover, double blind trial conducted by Li Pi Shan and Ashworth (2004), the two medications were studied in a mixed population (e.g., stroke and TBI). Participants received either lorazepam (0 to 1mg) or zopiclone (3.75 to 7.5 mg), which were taken if needed orally in the evening on a daily basis. At the end of study, little differences pertaining to sleep outcomes (e.g., length, depth or quality of sleep) were found between groups. The authors reported that zopiclone was equally effective as lorazepam in treating insomnia (Shan & Ashworth 2004). Due to less than 50% of the study population sustaining a brain injury, no level of evidence will be drawn from

this study. Additional studies, with a brain injury population, are needed before determining the effectiveness of lorazepam and zopiclone for insomnia post TBI.

15.5 Summary

Current research has focused on exploring and identifying sleep related issues post ABI but minimal research has focused on treatment interventions. Therefore, the results of this review provide little guidance to clinicians in the management of fatigue and sleep disorders post ABI. Cognitive behavioural strategies, such as energy conservation and pacing, that are commonly encouraged by health professionals have little published research evidence supporting their use. Pharmacological interventions for management of fatigue also appear to be under studied. Clinicians must rely on their individual clinical experiences/expertise when treating such issues. Utilizing research conducted in other patient populations may also be useful. Future research should focus on the management of fatigue and sleep disorder symptoms post ABI.

15.6 Conclusions

1. *There is level 3 evidence that those who sustain a TBI report greater levels of fatigue post injury.*
2. *There is Level 3 evidence to suggest that higher levels of fatigue may lead to a poorer quality of life.*
3. *There is Level 3 evidence, based on one study, that individuals who sustain a TBI do experience greater levels of fatigue and a decrease in vigilance, compared to those without an injury.*
4. *There is Level 4 evidence, based on one study, to suggest that cognitive behavioural therapy may assist in treating insomnia and help in the management of fatigue post TBI.*
5. *There is Level 2 evidence to suggest acupuncture is effective in improving perception of sleep and sleep quality in those who sustain a TBI.*
6. *There is level 1b evidence, from a single study, that blue light therapy is effective in reducing fatigue and daytime sleepiness during treatment.*
7. *There is Level 1a evidence that Modafinil is not effective in treating fatigue but has been shown to be effective short-term in treating excessive daytime sleepiness post ABI.*
8. *There is Level 3 evidence, based on a single study, that methylphenidate does not have an adverse effect on the sleep-wake cycle of those who have sustained a TBI.*

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